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Tuompo, Riitta

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Yersinia enterocolitica biotype 1A: a possible new trigger of reactive arthritis

Riitta Tuompo[1,5] · Timo Hannu[2] · Elisa Huovinen[3] · Leila Sihvonen[4] · Anja Siitonen[4] · Marjatta Leirisalo-Repo[1]

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Abstract *Yersinia enterocolitica* (*YE*) biotype 1A is generally considered non-pathogenic, and the role of it in causing reactive musculoskeletal complications is unclear. We evaluated the capability of *YE* biotype 1A to induce reactive arthritis (ReA) and other reactive musculoskeletal symptoms. Analysis of self-reported musculoskeletal symptoms was supplemented with a telephone interview (with a permission to acquire copies of patient files from a local physician or hospital) and/or clinical examination of subjects with recent musculoskeletal symptoms after a positive stool culture for *YE*. The diagnoses of ReA and reactive tendinitis and enthesitis (ReTe) were defined as "definite" when based on clinical examination and/or on interview by phone and "probable" when based solely on the questionnaire. Of 120 subjects, who reported musculoskeletal symptoms, 100 were included in the final analysis. Among these 100 patients, 68% had *YE* biotype 1A, 16% *YE* bio/serotype 4, and 1% biotype 2 infection; the remaining 15% had different *YE*-like strains or a non-biotypable strain. Of the 21 patients with ReA and of the 14 patients with ReTe, the diagnosis was definite in 9 and 7 patients and probable in 12 and 7 patients, respectively. The clinical picture of ReA caused by *YE* biotype 1A was similar with other bio/serotypes of *YE*. The definite ReA due to *YE* biotype 1A occurred in middle-aged adults (5 men, 4 women) with the most frequently affected joints being the knees and ankles. We suggest that *YE* biotype 1A should be taken into account as a new trigger of ReA.

Keywords Infection arthritis · Reactive arthritis · Spondyloarthritis · *Yersinia enterocolitica*

Introduction

Yersinia enterocolitica (*YE*) is an enteropathogen causing foodborne infections. There are six different biotypes of *YE* (biotypes 1A, 1B, 2–5), of which biotypes 1B and 2–5 are considered pathogenic, while biotype 1A is generally considered non-pathogenic [1]. Each biotype can include several different serotypes, some of which occur in both biotype 1A and pathogenic biotypes [2]. Because biotype 1A has been isolated from stools of diarrheic patients, its potential pathogenicity has been discussed in the literature [2, 3].

In Finland, with a population of 5.4 million, about 600 cases of yersinosis (mean annual incidence 11.1/100,000) have been reported annually in recent years [4]. The mean annual incidence of yersinosis was 7.2/100,000 in 2001–2008 in Germany [5] and 1.2/100,000 in 1998–1999 in a survey from Northern America [6]. *YE* infections usually appear sporadically, but some outbreaks have been reported [7–9].

Typical clinical symptoms of acute *YE* infection include diarrhea, abdominal pain, and fever, occasionally also vomiting; mesenteric lymphadenitis and terminal ileitis can mimic

✉ Riitta Tuompo
riitta.tuompo@hus.fi

1 Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

2 Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland

3 Epidemiologic Surveillance and Response Unit, National Institute for Health and Welfare (THL), Helsinki, Finland

4 Bacteriology Unit, National Institute for Health and Welfare (THL), Helsinki, Finland

5 Department of Rheumatology, Inflammation Center, Helsinki University Central Hospital, PO 372, 00029 HUS Helsinki, Finland

acute appendicitis. Reactive arthritis (ReA), an inflammatory sterile arthritis, and erythema nodosum can occur after *YE* infection [10–14].

Studies on *YE*-related ReA have focused on the traditionally pathogenic serotypes O:3 and O:9 [10–12, 15]. Only one study found musculoskeletal complications, which the authors considered potentially related to *YE* biotype 1 [11]. Furthermore, Huovinen et al. reported recently symptoms related to ReA attributable to *YE* biotype 1A in 3% of study subjects [16].

The role of *YE* biotype 1A in causing reactive musculoskeletal complications is unclear. The aim of this clinical study was to investigate the clinical picture and severity of ReA and other musculoskeletal complications associated with gastrointestinal infection caused by *YE* biotype 1A and also compare, if the clinical picture differs from ReA caused by traditionally pathogenic *YE* biotypes.

Patients and methods

Study design

The study was carried out in collaboration with the National Institute for Health and Welfare (THL) as part of a case–control study investigating the clinical features and sources of *YE* infections [16]. The study protocol was approved by the Ethics Committees of the Hospital District of Helsinki and Uusimaa and THL.

In brief, all *Yersinia*-positive stool specimens (excluding *Y. pseudotuberculosis*) were collected from 10 clinical microbiology laboratories, which annually report approximately two-thirds of all Finnish *Yersinia* cases. Two hundred and ninety-five subjects were included in the aforementioned case–control study. They had all answered to a detailed questionnaire concerning abdominal and extra-abdominal symptoms related to *YE* infection, including questions on the presence and duration of musculoskeletal (painful and swollen joints, limitation of joint movement, pain in tendon insertions, low back pain, neck pain), urinary (dysuria, hematuria) and eye symptoms (redness without discharge, pain, photophobia), and uveitis. Also, possible visits to a physician or a hospital and the use of antimicrobials in relation to current *YE* infection were asked.

Of these 295 subjects, 120 (41%) who reported new musculoskeletal symptoms related to the current *YE* infection were included in the present study. We attempted to contact all these 120 subjects by the telephone for a detailed interview and to invite them to a clinical examination by a rheumatologist (RT). The phone interview included previous history of musculoskeletal diseases, a detailed history of the symptoms related to *YE* infection supplemented by a review of the questionnaire and a permission to acquire copies of patient files from a local physician or hospital, which were thoroughly reviewed. In addition, a detailed examination of joints and tendons was an essential part of the clinical examination. Blood specimen collected from clinically examined patients were screened for human leukocyte antigen (HLA)-B27, rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) (Fig. 1).

Diagnostic criteria

ReA was defined as the development of synovitis (swollen joint with pain or with painful movement) in a previously asymptomatic joint, or as inflammatory low back pain (low back pain that was worse at night) within the first 2 months after the gastrointestinal infection [17]. This definition of ReA fulfils the preliminary diagnostic criteria presented in the 4th international workshop on reactive arthritis in 1999 [18]. Reactive enthesitis and tendinitis (ReTe) was defined as the presence of tendinitis, heel or elbow pain, and limited movements of joints without joint swelling related to the current infection. Arthralgia (Alg) was defined as pain in a previously asymptomatic joint without swelling and with a normal range of movement of the joint. The diagnoses of ReA, ReTe, and Alg were defined as "definite" when based on clinical examination and/or on interview by phone with review of copies of patient files from a local physician or hospital and "probable" when based solely on the questionnaire. Subjects with previous rheumatologic diagnosis or degenerative musculoskeletal problems were excluded.

Statistical analysis

Proportional data were compared with the χ^2 test or with Fisher's exact test. The Mann–Whitney *U* test or Student's *t* test was applied in comparisons of continuous variables. Differences at the 5% level were considered statistically significant. Data were analyzed with the SPSS statistical software system, version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patients with musculoskeletal symptoms

Of the 120 patients with musculoskeletal symptoms, 58 patients (48%) were interviewed by telephone and 62 patients (52%) were not contacted by telephone and their data were collected solely from the questionnaire.

Of these 120 patients, 13 patients were excluded, because of degenerative musculoskeletal problems, five were excluded because of other rheumatic disease (rheumatoid arthritis 2, psoriatic arthritis 1, ulcerative colitis-related spondyloarthropathy 1, fibromyalgia 1), one was excluded

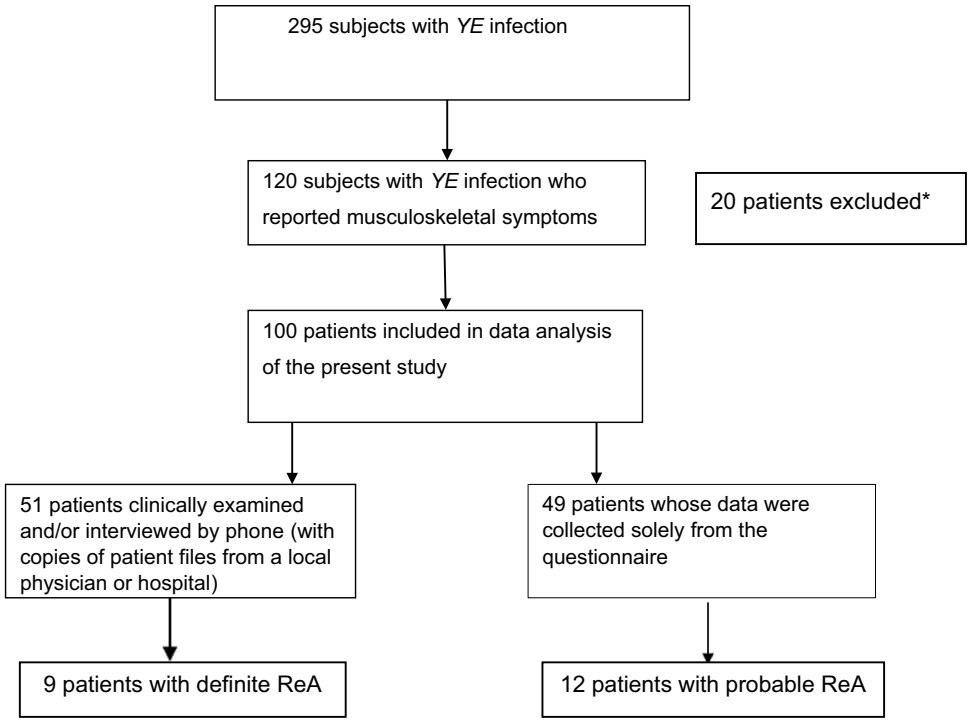

Fig. 1 Study flowchart. *ReA* reactive arthritis; *YE Yersinia enterocolitica.* *13 patients excluded because of degenerative musculoskeletal problems, 5 patients excluded because of other rheumatic disease, one patient excluded because Salmonellosis 3 months earlier, one patient excluded because musculoskeletal symptoms developed over 2 months after the gastrointestinal symptoms

because of *Salmonella* enteritis 3 months earlier and one was excluded because the musculoskeletal symptoms developed later than 2 months after the gastrointestinal symptoms.

After the exclusion, the present study comprises 100 patients. Of these, 51 were clinically examined and/or interviewed by phone and, in the remaining 49, data were based merely on the questionnaire. The mean age of these patients was 48.4 (range 20–89) years; 61 were females. There were no patients under the age of 16.

Of the 100 patients, 68 had *YE* biotype 1A, 17 had other *YE* bio/serotypes (4/O:3 $n = 16$, 2/O:9 $n = 1$), 14 had *YE*-like strain (*Y. frederiksenii* 7, *Y. kristensenii* 2, *Y. bercovieri* 2, *Y. intermedia* 2, *Y. mollaretii* 1), and 1 had a non-biotypable *YE* strain. The patient with the non-biotypable *YE* strain was analyzed among the biotype 1A group.

As features of *YE* infection, 82 reported diarrhea, 81 abdominal pain, and 15 vomiting. Symptoms related to the lower urinary tract were reported by 12 patients. Altogether 41 patients reported eye symptoms. Two patients had uveitis, one of them with *YE* biotype 1A infection and the other with *Y. frederiksenii* infection; both of these patients also had ReA. One patient with *YE* biotype 1A infection reported erythema nodosum.

Reactive musculoskeletal symptoms

Of the 100 patients, 84% reported joint pain, low back pain was reported by 59%, pain on joint movement by 58%, joint swelling by 28%, and 19% reported warmness/redness of the joint. Twenty-nine patients (29%) had visited a local doctor because of musculoskeletal symptoms.

Of the 100 patients with musculoskeletal symptoms, 21 (21%) fulfilled the criteria for ReA and an additional 14 (14%) for ReTe. None of the patients with ReA had ReTe, and none of the patients with ReTe had ReA. The diagnosis remained arthralgia in 65 patients (65%). Of these 21 patients with ReA, the diagnosis was definite (confirmed with clinical examination and/or telephone interview with review of copies of patient files from a local physician or hospital) in 9 and probable (based solely on data of the questionnaire) in 12 patients. Of the 14 patients with ReTe and of the 65 patients of arthralgia, the diagnosis was definite in 7 and 35 patients and probable in 7 and 30 patients, respectively. The distribution of musculoskeletal symptoms occurring after infection of different bio/serotypes of *YE* is shown in Table 1. The clinical picture of ReA caused by *YE* biotype 1A was similar with other bio/serotypes of *YE* (data not shown).

Patients with definite *YE* triggered ReA

The clinical picture of nine patients with definite ReA is shown in Table 2. They were all adults (5 men, 4 women) with a mean age of 49 (range 27–76) years. The most frequently affected joints were the knees and ankles, followed by small joints of the hands, and wrists. Of extra-articular features, one patient had uveitis. The clinical picture of definite ReA did not differ from that of probable ReA (data not shown).

Table 1 Distribution of definite or probable reactive musculoskeletal symptoms in patients ($n = 100$) after infection of different bio/serotypes of *Yersinia enterocolitica* verified by stool culture

YE bio/serotype	Patient group	ReA	ReTe	Alg
1A	Definite	6 (18)	2 (6)	25 (76)
	Probable[a]	10 (28)	4 (11)	22 (61)
2/O:9	Definite	0	0	0
	Probable	0	0	1 (100)
4/O:3	Definite	2 (22)	3 (33)	4 (45)
	Probable	2 (29)	3 (42)	2 (29)
YE-like strain	Definite	1 (11)	2 (22)	6 (67)
	Probable	0	0	5 (100)
Total	Definite	9 (18)	7 (14)	35 (68)
	Probable	12 (25)	7 (14)	30 (61)
	All	21 (21)	14 (14)	65 (65)

Definite, diagnosis confirmed with clinical examination and/or telephone interview with review of copies of patient files from a local physician or hospital

Probable, diagnosis based solely on data of the questionnaire

Values are presented as *n* (%) or *n*

Alg arthralgia, *ReA* reactive arthritis, *ReTe* reactive enthesitis and tendinitis, *YE Yersinia enterocolitica*

[a]One patient with non-biotypable *YE* strain

Table 2 Clinical picture of 9 patients with definite reactive arthritis triggered by different *Yersinia enterocolitica* biotypes

	YE biotype 1A	*YE* biotype 4 (serotype O:3)	*YE*-like strain *Y. frederiksenii*
Number of patients	6	2	1
Age, years, mean (range)	46 (27–61)	37 (30–44)	45
Gender, male/female	5/1	0/2	0/1
Distribution of affected joints, *n* (%)			
Shoulder	1 (17)	0	0
Elbow	2 (33)	0	0
Wrist	2 (33)	0	0
Fingers	2 (33)	1 (50)	1 (100)
Knee	4 (67)	0	0
Ankle	4 (67)	0	0
Feet	1 (17)	1 (50)	1 (100)
Low back pain, *n* (%)	2 (33)	1 (50)	1 (100)
Patients with extra-articular features, *n* (%)			
Uveitis	1 (17)	0	1 (100)
Urethritis	1 (17)	0	0

YE Yersinia enterocolitica

Clinical examination

Of the 100 patients, 14 participated in the clinical examination. The patients were seen a mean (median) of 30 (30) (range 28–34) months after the positive stool samples were taken. The musculoskeletal symptoms had mainly resolved by the clinical examination. One HLAB27-positive patient who had ReA had still tenderness in the sacroiliac joints. This patient, who had had *Y. frederiksenii* in the stool culture, had also suffered from uveitis in the acute phase of the disease.

The prevalence of HLA-B27 was 25% (1 of 4) among patients with ReA, 0% (0 of 1) among patients with ReTe, and 33% (3 of 9) among patients with arthralgia. None of the patients tested were positive for RF, and the mean values for CRP and ESR were within normal limits.

Discussion

As far as we know, this is the first study to show that *YE* biotype 1A can trigger ReA. ReA occurred in middle-aged subjects and not only affected predominantly the joints of the lower extremities (knees, ankles), but also the wrists and small joints of the hands. One patient had uveitis and one patient suffered from urethritis, both of which are well-known extra-articular features of ReA [19]. Urethritis as an extra-articular manifestation of ReA has been described also in cases triggered by gastrointestinal infection, such as *Yersinia* [12] and *Salmonella* [20]. It is also possible that our patient had urethritis due to *Chlamydia trachomatis* infection but we could not exclude this because Chlamydia was not investigated. One patient also had erythema nodosum, a complication typically associated with *Yersinia* infection [21]. Taken together, the clinical characteristics of ReA triggered by *YE* biotype 1A were similar to those of ReA caused by other *Yersinia* bio/serotypes in the present series or described in the literature [12, 22–24].

Our series was based on the study by Huovinen et al., which reported prevalence of symptoms of ReA in an epidemiological study [16]. No data on clinical examination was reported in that study, but the clinical rheumatological findings are presented for the first time in the current study. Also, the diagnosis of probable ReA was defined more broadly in the case–control study by Huovinen et al., whereas we applied in the present study more strictly diagnostic criteria of ReA used previously by us in several studies [17, 25–29].

Previous investigations of *YE*-related ReA have concentrated on the traditionally pathogenic serotypes O:3 and O:9 [10–12, 15] or the exact *Yersinia* bio/serotype is not reported [30]. Only one previous study from England has described musculoskeletal complications potentially related to *YE* biotype 1 [11]. In that study, exacerbations of spinal and

peripheral joint symptoms and a significant rise of ESR were seen in patients with pre-existing ankylosing spondylitis, of whom *YE* biotype 1 was isolated in fecal culture. Of note, no clinical cases of ReA were presented.

All except one patient had recovered from reactive joint complications by the time of the clinical examination. The time period between the beginning of the musculoskeletal symptoms and the clinical examination was long, but it enabled us to show the outcome of reactive arthritis, which was favourable. This is in line with previous reports with ReA triggered by *Shigella* [27] or *Campylobacter* [17]. According to the literature the long-term prognosis of ReA triggered by *YE* infection is also usually good. In a 10-year follow-up study of patients with *YE*-induced ReA, 5.9% developed chronic peripheral arthritis and 35.3% had inflammatory back pain associated with HLAB27-positivity [14]. None of our patients with reactive joint symptoms were aged under 16 years, which is consistent with previous reports, indicating that ReA is infrequent among children [25, 29, 31].

The pathogenicity of *YE* is usually associated with bio/serotypes 2–3/O:9, O:5, and 4/O:3. Also biotype 1B is considered highly pathogenic, but it is infrequently found in Europe [1]. In addition to the *Yersinia* virulence factor plasmid (pYV), the pathogenic strains have other virulence genes (*inv*, *ail*, *ystA* and *myfA*) [3]. Because the known *Yersinia* virulence factor plasmid (pYV) is missing in *YE* biotype 1A, this biotype has been assumed to be avirulent. Of the virulence genes of *Yersinia enterocolitica* strains, *YE* biotype 1A carries *inv* and *hreP* genes, but not *ystA* and *virF* [32]. The absence of major virulence determinants, especially *ail*, in *YE* biotype 1A has been interpreted to indicate that biotype 1A strains are non-pathogenic to humans. Recently, biotype 1A strains have been shown to have high genetic diversity [33], and 2% *YE* biotype 1A strains have been found to be *ail* positive [34].

For the development of ReA, the triggering infection, e.g. *Yersinia* in the gut, invades the mucosa and persists in the host either in the epithelium or within associated lymphoid tissues. The microbe is disseminated in the joint, where it causes inflammatory response. *Yersinia* heat shock protein 60 and 19 kd protein of *Yersinia* urease induce T cell responses in inflamed joint [35, 36]. The patient responds with cytokine imbalance with a relative lack of T-helper cytokines, which may permit the persistence of the triggering microbe [37]. While often considered apathogenic, *YE* biotype 1A is capable of adhering to and invading epithelial cells and of surviving within macrophages. Human isolates of *YE* biotype 1A are also able to induce secretion of pro-inflammatory cytokines (IL-6, IL-8 and TNF) from macrophages [38].

The *Yersinia* adhesin (yadA) has also suggested to play a role in the development of ReA. In experimental animal studies, yadA positive *YE* serotype O:8 induced arthritis in rat [39]. YadA shares a linear tetrapeptide with HLA-B27, and antibodies against synthetic peptide including HLA-B27 homologue sequences of yadA were observed in one-third of patients with HLA-B27 associated diseases [40]. The role of yadA in the development of arthritis in our patients in the present series has to be rejected, however, as the *YE* biotype 1A strains do not have yadA [32], even in the case if the strain harbors *ail* gene [41].

Definitive diagnosis of *YE* infection as a causative agent for ReA is best achieved by a positive culture of the microorganism [42]. Cold enrichment seems to increase the number of positive biotype 1A cases. It increased the findings of biotype 1A strains by 72% and of 4/O:3 and 2/O:9 strains by 25% [43]. While cold enrichment is not frequently used for human clinical samples in all countries [34, 43], it is particularly useful for ReA cases, when the patient is no longer diarrheic and there could be a low concentration of causative pathogens in the stool sample. The measurement of antibodies against *YE* in sera is another option for establishing the causative agent in ReA. Antibodies of IgM class appear soon after the onset of infection and persist in the sera for 1–3 months. IgG and especially antibodies of IgA class may persist for several months to years in sera of patients after postinfectious arthritis caused by *YE* [44]. However, the accuracy of associations between serologic findings and clinical conclusions is hampered by poor standardization of serologic methods [45].

Methodologically, the questionnaire-based approach is usually the only relevant method to conduct population-based studies. Our study group has previously used this methodology successfully in several large studies [17, 25–28]. Furthermore, our results were based not only on information from the questionnaire but complemented in half of the cases with a telephone interview (with copies of patient files from a local physician or hospital) and also with a clinical examination. ReA was slightly more diagnosed if the analysis was based only on the information reported in the questionnaire compared with the interview and clinical examination. However, the clinical picture of definite ReA did not differ from that of probable ReA.

There are limitations in our study. The proportion of the patients taking part to the clinical examination was smaller than expected. Also the time-period between the acute infection and the clinical follow-up was long. It might have been interesting to study the IgM, IgG, and IgA class antibodies and their persistence in subjects with or without musculoskeletal symptoms. Because of the epidemiological setting of the study, this was not, however, possible. The presented results can be considered preliminary and impose the need for further studies.

In conclusion, our study provides new evidence of arthritogenicity of *YE* biotype 1A. We suggest that it should be taken into account as a new trigger of ReA, but extensive

research is warranted to elucidate our findings in future studies.

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Compliance with ethical standards

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Conflict of interest Author Riitta Tuompo has received research grants from Scandinavian Rheumatology Research Fund and Finnish Rheumatology Research Fund and Helsinki University Central Hospital Fund. Author Marjatta Leirisalo-Repo has received grant from Helsinki University Hospital Funds and consultancy fees from Pfizer, Lilly and Boehringer Ingelheim and payment for lectures from Roche and BristolMyersSquibb. Author Timo Hannu declares that he has no conflict of interest. Author Elisa Huovinen declares that she has no conflict of interest. Author Leila Sihvonen declares that she has no conflict of interest. Author Anja Siitonen declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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